Remarks/Arguments:

Claims 1-2, 4-5, 7-13, 15-18, 20-21, and 23-24 are pending in the application. Reexamination and reconsideration of the application are respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 102

1. Claims 1-2, 5, 7-13, 16-18, 20-21, and 23-24 are rejected under 35 USC § 102(e) as being anticipated by US 6,673,541 to Klein et al. ("Klein"). Applicants respectfully traverse.

Among the rejected claims, claims 1, 7, 9, 11, 13, 16-18, 20, and 23 are independent claims. All these claims require detection of DNA markers in a cell-free bone marrow sample.

In contrast, Klein discloses a method of amplifying cellular DNA in bone marrow aspirates. For example, at column 6, lines 32-40, it is stated:

> In a preferred embodiment of the method of the present invention DNA which is amplified is the genome of a single cell or chromosomes or (a) fragment(s) thereof. It has surprisingly been found that the method of the present invention is particularly useful for the analysis of single cells such as disseminating tumor cells, cells obtained from a lymph node, peripheral blood cells, cells from bone marrow aspirates, cells from tumor biopsis, cells obtained from microdissected tissue, or the like. (emphases added)

At column 16, lines 45-67, it is stated:

> The extremely rare individual tumor cells in bone marrow were identified in marrow aspirates by indirect immunofluorescence with the monoclonal cytokeratin antibody A45 B/B3 (Micromet)...
>
> Aspiration of the bone marrow samples and isolation of mononucleated cells was performed as described (Pantel (1996), Lancet 347, 649-653)...
>
> ...Bone marrow cells were plated at a density of 250,000 cells/0.8 cm^2 in a volume of 200 µl on a microscope slide... (emphases added)

At column 17, lines 1-18, it is stated:

> ...a single immunofluorescence-labeled cell detected among unstained bone marrow cells, was picked by micromanipulation and transferred to a new slide for visual control that no additional cell was inadvertently aspirated (FIG. 4A-C). From this slide the cell was taken to the final reaction tube. FIG. 4D depicts the chromosomal gains and losses found by CGH analysis in this cell that were consistent with chromosomal imbalances reported earlier for breast cancer... (emphases added)

Since Klein discloses nothing about detecting DNA markers in a cell-free bone marrow sample, it cannot anticipate claim 1, 7, 9, 11, 13, 16-18, 20, or 23. By the same token, claims 2 and 5 (dependent from claim 1), 8 (dependent from claim 7), 10 (dependent from claim 9), 12 (dependent from claim 11), 21 (dependent from claim 20), and 24 (dependent from claim 23) are also novel over Klein. Withdrawal of the rejections is thus respectfully requested.

2. Claims 1-2, 5, 7-13, 16-18, 20-21, and 23-24 are rejected under 35 USC § 102(b) as being anticipated by WO 00/17390 to Klein et al., as represented by US 6,673,541 to Klein et al. Applicants respectfully traverse as discussed above.

CLAIM REJECTIONS UNDER 35 USC § 103

Claims 4 and 15 are rejected under 35 USC § 103(a) as being unpatentable over Klein in view of Silva et al. (2002) Ann. Surg. Oncol. 9(1):71-76 ("Silva"). Applicants respectfully traverse.

Claim 4 depends from claim 1; claim 15 is an independent claim. Both claims 1 and 15 require detection of DNA markers in a cell-free bone marrow sample. As discussed above, Klein discloses a method of amplifying cellular DNA in bone marrow aspirates, and therefore fails to teach every limitation of claim 1 or 15. Silva cannot cure the defect of Klein, and was not relied on for such. Instead, Silva was relied on for disclosing various DNA markers. However, even if one skilled in the art would have been motivated to combine the method of Klein with the DNA markers taught by Silva as suggested by the Examiner (which Applicants do not

concede to for the reasons to be discussed below), such combination does not add up to the present invention. That is, the combination at best would result in a method of amplifying cellular DNA markers in bone marrow aspirates, not a method of detecting acellular DNA markers in a cell-free bone marrow sample.

Further, Silva discloses detecting acellular DNA in blood plasma samples (see, e.g., page 73, right column, first paragraph under subheading "Tumor and Plasma DNA Alteration Before Mastectomy," lines 3-7; page 74, left column, first paragraph under subheading "Plasma DNA Alterations After Mastectomy," lines 1-8). Since the methods of Klein and Silva target different types of DNA (cellular DNA versus acellular DNA) in different types of samples (bone marrow aspirates versus blood plasma), one skilled in the art would not have been motivated to combine the two references, because substituting cellular DNA in bone marrow aspirates with acellular DNA in blood plasma would frustrate the purpose of the method of Klein.

In light of the foregoing, Klein and Silva, either alone or in combination, do not render claim 1 or 15 obvious. Claim 4 is also non-obvious over the cited art for at least the same reasons. Therefore, Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned at the Los Angeles, California telephone number (310) 785-4600 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Date: January 30, 2009

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